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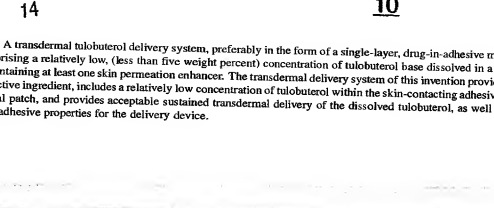
(54) Title: TRANSDERMAL TULOBUTEROL DELIVERY SYSTEM, METHOD AND COMPOSITION THEREFOR



(57) Abstract: A transdermal tulobuterol delivery system, preferably in the form of a single-layer, drug-in-adhesive matrix patch, is disclosed comprising a relatively low, (less than five weight percent) concentration of tulobuterol base dissolved in a skin adhesive composition containing at least one skin permeation enhancer. The transdermal delivery system of this invention provides controlled release of the active ingredient, includes a relatively low concentration of tulobuterol within the skin-contacting adhesive formulation of a transdermal patch, and provides acceptable sustained transdermal delivery of the dissolved tulobuterol, as well as acceptable tack and. peel adhesive properties for the delivery device.

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TRANSDERMAL TULOBUTEROL DELIVERY SYSTEM, METHOD AND COMPOSITION THEREFOR

Cross-Reference to Related Application

This application claims the priority of U.S. Provisional Application for Patent Serial No. 60/518,124 filed November 7, 2003, which is incorporated herein by reference.

Technical Field of the Invention

This invention relates generally to drug delivery systems, and more particularly, to the transdermal delivery of tulobuterol, a transdermal composition and method therefor.

Background of the Invention

Tulobuterol is a $ß_2$-adrenergic receptor agonist widely used in the treatment of acute bronchitis, chronic bronchitis, bronchial asthma, pulmonary emphysema, and like respiratory conditions to relieve dyspnea of patients suffering from bronchoconstriction. Tulobuterol is a recognized bronchodilator that acts selectively at a $ß_2$-receptor of the sympathetic nervous system to relax the bronchial smooth muscles.

Tulobuterol is generally administered through oral routes, in the form of tablets, syrups, lozenges, and the like, or through the airway delivered in aerosolized form, typically with a metered-dose inhaler. Oral dosages, however, are difficult to administer to infants, feeble or elderly persons, and are associated with side effects caused by steep increases of the drug concentration in the blood, a brief period of therapeutic efficacy, and the like. Aerosolized forms present misuse problems, such as incorrect or excessive inhalation, and in some cases are associated with a higher risk of death.

Topically applied dosage forms, such as ointments, creams, and the like, can avoid the undesirable temporary increases of tulobuterol blood levels associated with oral administration, but such externally applied dosage forms are

easily removed by clothing, making it difficult to control effecting the therapeutic dosage.

There is an ongoing need and desire, therefore, for a controllable, safe, easy-to-use drug delivery forms that can provide a sustained rate of drug release. Transdermal drug delivery systems in the form of patches or tapes containing medicaments have been developed and are rapidly gaining in popularity and increasing usage.

A general discussion of transdermal drug delivery patch systems, measurement of skin permeation, and methods of manufacturing conventional transdermal patch devices is found in Cleary, Chapter 11, entitled "Transdermal Drug Delivery," in Zatz Ph.D. (ed.), *Skin Permeation Fundamentals and Application*, pp 207-237, published by Allured Publishing Corporation, Carol Stream, IL (1993), the relevant disclosures of which are incorporated herein by reference.

The use of a transdermal composition, for example, a pressure-sensitive adhesive containing a drug, as a means of controlling drug delivery through the skin at essentially a constant rate, is well known. Such known delivery systems generally incorporate the medicament into a carrier such as a polymeric matrix and/or a pressure-sensitive adhesive formulation. The pressure-sensitive adhesive must adhere effectively to the skin and permit migration of the medicament from the carrier through the skin and into the bloodstream of the patient.

Percutaneous absorption type preparations containing tulobuterol in tape formats have been developed. U.S. Patent No. 5,571,530 describes a percutaneous preparation of tulobuterol dissolved or dispersed in a pressure-sensitive adhesive base layer composed of polyisobutylene rubber mixtures with no percutaneous penetration enhancers, carriers, or the like, to minimize interaction between the base layer and tulobuterol and thereby improve drug stability. Although amounts of from 1 to 50% by weight of tulobuterol in the adhesive layer are reported, blood level efficacy and sustained efficacy was generally lower, over a period of 4 hours, than that of orally administered tablets of tulobuterol in comparative studies with tapes having a tulobuterol content of 5%, 10% and 20% by weight in the adhesive layer.

Some attempts have been made to control the rate of permeation of tulobuterol through the skin by using a drug reservoir system of tulobuterol crystals. U.S. Patent No. 5,639,472, for example, discloses tape preparations containing tulobuterol in a plaster layer in which tulobuterol is present in a concentration of not lower than the solubility of the drug in the adhesive, and the ratio of dissolved tulobuterol to crystalline tulobuterol is from 0.1 to 10. In general, increasing the tulobuterol content dissolved in a plaster layer is considered to lead to a higher percutaneous absorption rate of the drug, and to lead to a longer duration of drug release. Keeping tulobuterol in a dissolved state at a high concentration and stable in the polymeric adhesive medium used to form a plaster layer is generally difficult to achieve. For satisfactory percutaneous absorption rate and sustained release of tulobuterol, therefore, the total drug content is generally contained in a plaster layer at a concentration of not less than the solubility of the drug in the adhesive, and part of the drug load is intentionally present in a crystalline state in the plaster layer, as taught in, for example, U.S. Patent No. 5,639,472.

U.S. Patent No. 6,117,447 discloses a percutaneous absorption preparation comprising a support and plaster layer laminate comprising not less than 5 weight %, based on the weight of the plaster tulobuterol dissolved in an adhesive composition. A commercially available transdermal therapeutic system for bronchial asthma that embodies a reservoir of crystalline tulobuterol and percutaneous absorption preparations described in one or more of U.S. Patents No. 5,639,472 and No. 6,117,447, is sold under the trademark HOKUNALIN® Tapes by Hokuriku Seiyaku Co., Ltd., Japan. These commercial tapes are available as patches for dosages amounts of 0.5 mg, 1 mg, and 2 mg tulobuterol to use, respectively, for children from 6 months to less than 3 years of age, children from 3 to less than 9 years of age, and children of 9 years of age and older. The crystal reservoir of the commercial tape is intended to have a long lag-time, so the patches are attached to the skin of the chest, back or upper arm once a day at bedtime to provide peak drug levels in the morning. Thus, the commercial tape is intended to treat "morning-dip" bronchial asthma attacks, especially in children, that occur as a result of low cortisol levels and low inhaled bronchodilator drug levels.

Preparations containing solid drug crystals in the plaster layer, however, are susceptible to precipitation of the drug crystals on the surface of the plaster layer where it comes into contact with the skin, thus undesirably degrading the adhesive property to the skin. Inasmuch as the diffusion rate of tulobuterol in the polymeric adhesive medium is markedly slower than that in a liquid medium, the drug crystals gradually precipitate in the plaster layer over time. Gradual crystallization of the drug in the plaster layer is expected to adversely influence the adhesive property of the preparation to the skin and drug releasing property over time. When the drug is contained at a concentration of not less than the solubility thereof in the adhesive, the preparation containing part of the drug in a crystalline state in the plaster layer may fail to provide sufficient stability of the preparation quality. This poses considerable problems for achieving optimum percutaneous absorption, maintaining sustained duration of the efficacy and achieving optimum adhesion to the skin of the preparation.

Additionally, reservoir patches have many disadvantages. Reservoir patches, because of the volume of the reservoir contents, and construction, are normally physically and visually bulky, and are cosmetically unacceptable to many patients as the patch is not flush with the skin surface when applied. Another disadvantage is that the adhesive area is limited to the periphery of the effective drug area of the patch and generally does not adhere well to the skin.

There is still a need and desire for a transdermal drug delivery system that provides effective and sustained release of tulobuterol at relatively low concentrations of tulobuterol, i.e., less than 5 weight percent of the drug in the drug/adhesive formulation, to minimize side effects without sacrificing efficacy or adhesive stability. The present invention provides such a transdermal drug system.

Summary of the Invention

The present invention provides a transdermal tulobuterol delivery system comprising a composition containing less than 5 weight percent tulobuterol dissolved in an adhesive medium, and a method for transdermal delivery of a bronchodilating effective amount of tulobuterol upon application of the transdermal system to the surface of human skin. A preferred transdermal tulobuterol delivery system is a single-layer, drug-in-adhesive matrix patch system.

A preferred transdermal skin adhesive composition comprises a therapeutically effective amount of less than 5 weight percent total tulobuterol, on a total composition weight basis, dissolved in at least one physiologically tolerable adhesive, and preferably at least one skin penetration enhancer.

A preferred transdermal tulobuterol delivery patch comprises an inert impermeable backing film having a therapeutically effective amount of skin adhesive composition of the invention coated thereon. Preferably, the patch includes a protective release liner laminated to the skin contacting surface of the skin adhesive composition and through which the tulobuterol is not permeable. For use, the release liner is removed and the skin adhesive face of the patch is placed in contact with a skin surface, such as the skin of the chest, back or upper arm.

A particularly preferred transdermal tulobuterol composition comprises, on a total drug-in-adhesive matrix composition weight basis,

tulobuterol base in the range of about 1 to about 4.9 weight percent,

at least one skin penetration enhancer in a total amount in the range of about 0.1 to about 40 weight percent, preferably in the range of about 5 to about 20 weight percent, and

the remainder comprising an effective skin adhesive amount of at least one polymeric pressure-sensitive adhesive.

Preferred adhesives can be acrylic acid based, rubber based, silicone based or combinations thereof.

A preferred transdermal tulobuterol patch has an active surface area size in the range of about 2.5 to about 10 square centimeters, a drug loading of not more than about 0.2 milligrams per square centimeters, and a drug delivery rate of about 7.5 micrograms per square centimeters per hour.

Surprisingly, patch embodiments of tulobuterol containing skin adhesive compositions of this invention maintain a relatively low (i.e., less than 5%) content of tulobuterol in a dissolved state (i.e., no apparent crystalline tulobuterol in the adhesive matrix), and were judged substantially equivalent, in % drug release and in rate of permeation through skin, to conventional transdermal preparations having a relatively high (i.e., not less than 5%) content of tulobuterol. The transdermal tulobuterol compositions and delivery system provide controlled

release of the active ingredient and can be produced by a variety of methods known in the preparation of drug-in-adhesive preparations, including the mixing of an adhesive, drug, and additional excipient ingredients in solution, followed by removal of the processing solvents.

Brief Description of the Drawings

In the drawings,

FIG. 1 is a schematic illustration of a transdermal tulobuterol delivery patch of the present invention represented as a single-layer drug-in adhesive delivery system; and

FIG. 2 is a graphical representation of % release of tulobuterol from two transdermal tulobuterol delivery systems of the invention compared to that of a commercial product over a period of about 24 hours.

Detailed Description of Preferred Embodiments

The terms "transdermal patch" or "patch" as used herein includes structures in the form of tapes, strips, sheets, dressings or any other like form known to those skilled in the art, without limitation as to dimensional size or construction, except where specifically indicated, that can be applied to the skin of a mammal. A preferred transdermal tulobuterol system embodiment, without being limited thereto, has a single-layer, drug-in-adhesive (DIA) patch anatomy, characterized by the inclusion of the drug directly within the skin-contacting adhesive medium rather than as a separate layer. In this type of transdermal patch embodiment, the adhesive medium serves to both affix the bronchodilator system device to the skin and as the formulation foundation containing the drug and all excipients, and is applied as a substantially coterminous coating on a backing support film or layer. The terms "skin adhesive composition," "drug-in-adhesive matrix," or "DIA matrix" are used interchangeably herein to refer to the drug-containing adhesive medium of the transdermal patch. A polymeric pressure sensitive skin adhesive medium is preferred.

Tulobuterol is a beta-2 agonist used as a bronchodilator for the treatment of bronchial asthma, acute bronchitis, chronic bronchitis, and pulmonary emphysema. Tulobuterol is designated chemically as

2-chloro-α-[[(1,1-dimethylethyl)amino]methyl]benzenemethanol, has a molecular weight of 227.73, and the molecular formula: $C_{12}H_{18}ClNO$. Crystals of tulobuterol have a reported melting point in the range of about 89 to about 93 °C. Tulobuterol is available in the free base form or as a hydrochloride salt. Crystalline tulobuterol hydrochloride powders have a reported melting point in the range of about 161 to about 163 °C. The term "tulobuterol", as used herein, includes the free base form of this compound, as well as chemotherapeutically acceptable acid addition salts thereof.

Without limitation thereto, tulobuterol base is preferred for use in practicing the present invention and will be referred to for convenience as "tulobuterol". Tulobuterol base is commercially available from Oharu Chemical (Osaka, Japan).

Transdermal tulobuterol delivery system embodiments of this invention provide tulobuterol dissolved in a physiologically tolerable adhesive and maintained in dissolved (i.e., non-crystalline) form therein. The amount of tulobuterol incorporated into the adhesive medium of the skin adhesive composition varies with the desired therapeutic dosage effect and the time period over which the drug delivery system patch is to provide therapy. The amount of tulobuterol base content in the skin adhesive composition, on a drug-in-adhesive matrix composition weight basis is less than 5%, and preferably may be in the range of about 1 to about 4.9%, more preferably in the range of about 2 to about 4.5%. Surprisingly, the transdermal tulobuterol delivery system of this invention having a tulobuterol content of less than 5% in the skin adhesive composition provided skin permeation equivalent to or greater than that provided by conventional transdermal delivery systems having a tulobuterol content of not less than 5% in the adhesive layer.

A preferred composition of the drug delivery system also contains at least one skin penetration enhancer, and more preferably at least two skin penetration enhancers. Agents that accelerate the delivery of the drug through the skin are referred to in the art as skin-penetration enhancers, accelerants, adjuvants, and sorption promoters, and are collectively referred herein as "skin penetration enhancers."

A preferred transdermal tulobuterol patch embodiment for daily dosage intervals has an active drug area size in the range of about 2.5 to about 10 square centimeters (cm^2), a drug load of about 0.2 milligrams (mg)/cm^2, a drug content of less than 5 weight percent, based on the weight of the drug-in-adhesive matrix, a drug flux rate of about 7.5 micrograms/cm^2/hour, and is substantially free of tulobuterol crystals in the adhesive matrix. A particularly preferred transdermal tulobuterol patch has an active drug release area size in the range of about 10 cm^2, a drug concentration of about 4.5 weight %, a drug assay in the range of about 1.8 to about 2.2 mg of tulobuterol per patch, and has a translucent appearance with no discoloration or signs of crystallization.

A general discussion of transdermal patch drug delivery systems, measurement of skin permeation, and methods of manufacturing conventional transdermal patch devices is found in Cleary, Chapter 11, entitled "Transdermal Drug Delivery," and general discussion of various skin penetration enhancers is in Rieger, Chapter 2, entitled "Factors Affecting Sorption of Topically Applied Substances," both found in Zatz Ph.D. (ed.), *Skin Permeation Fundamentals and Application*, pp. 33-72, published by Allured Publishing Corporation, Carol Stream, IL (1993), the relevant disclosures of which are incorporated herein by reference. A detailed description of transdermal drug delivery systems, skin penetration enhancers and adhesives is also given in U.S. Patent No. 6,235,306 B1, the disclosures of which are incorporated herein by reference.

The penetration enhancer is present in an amount sufficient to enhance the penetration of the tulobuterol. The specific amount of skin penetration enhancer varies necessarily according to the desired release rate. The amount of total skin permeation enhancer in the skin adhesive composition, on a total composition weight basis, may be in the range of about 0.1 to about 40%, more preferably in the range of about 5 to about 20%, most preferably in the range of about 1 to about 15%. Particularly preferred were combinations of at least two skin permeation enhancers. When combinations are used, each skin permeation enhancer may be in the range of about 0.05 to about 5%, more preferably in the range of about 0.5 to about 20%, based on the total weight of the skin adhesive composition.

In general, suitable penetration enhancers can be chosen from alcohols, carboxylic acids, carboxylic esters, polyols, amides, surfactants, terpenes, alkanones, organic acids, solvents, and mixtures thereof. See generally Chattaraj, *et al.*, "Penetration Enhancer Classification", pp. 5-20 in Maibach, *et al.* (eds.), *Percutaneous Penetration Enhancers*, CRC Press, Inc., Boca Raton, FL (1995), Büyüktimkin, N., *et al.*, "Chemical Means of Transdermal Drug Permeation Enhancement," in Ghosh, T.K., *et al.*, (eds.) *Transdermal and Topical Drug Delivery Systems*, Interpharm Press, Inc., Buffalo Grove, IL (1997), the relevant disclosures of which are incorporated herein by reference.

Suitable aliphatic alcohols include, without limitation thereto, ethanol, propanol, butanol, pentanol, hexanol, octanol, nonanol, decanol, 2-butanol, 2-pentanol, benzyl alcohol, caprylic alcohol, decyl alcohol, lauryl alcohol, 2-lauryl alcohol, myristyl alcohol, cetyl alcohol, stearyl alcohol, oleyl alcohol, linolyl alcohol, linolenyl alcohol and mixtures thereof. Lauryl alcohol is preferred. Suitable aromatic alcohol is benzyl alcohol and the like.

Non-limiting examples of suitable carboxylic acids include fatty acids, such as caproic, capric, caprylic, lauric, myristic, palmitic, stearic, isostearic acid, oleic, linoleic, linolenic, and the like; and other straight-chain or branched organic acids, such as valeric, heptanoic, pelargonic, isovaleric, neopentanoic, neoheptanoic, neononanoic, trimethyl hexanoic, neodecanoic and mixtures thereof. Oleic acid is preferred.

Non-limiting examples of suitable carboxylic esters include sorbitan derivatives, such as sorbitan laurate (SPAN® 20), sorbitan oleate (SPAN® 80), and the like; esters of C_6-C_{22} carboxylic acid, such as isopropyl myristate, isopropyl palmitate, octyldodecyl myristate, ethyl oleate, ethyl laurate, isopropyl n-hexanoate, isopropyl n-decanoate, isopropyl n-butyrate, methylvalerate, methylpropionate, diethyl sebacate, and the like; and acetates, such as ethyl acetate, butyl acetate, methyl acetate, and the like, and mixtures thereof. Ethyl acetate is preferred.

Non-limiting examples of suitable polyols include propylene glycol, polyethylene glycol (PEG), ethylene glycol, diethylene glycol, triethylene glycol (TEG), dipropylene glycol, glycerol, propanediol, sorbitol, isosorbitol, dextrans,

butanediol, pentanediol, hexanetriol, and mixtures thereof. Propylene glycol and TEG are preferred.

Suitable surfactants include, without limitation thereto, anionic surfactants, cationic surfactants, nonionic surfactants, amphoteric surfactants, bile salts and lecithin. Example anionic surfactants include sodium laurate, sodium lauryl sulfate, and mixtures thereof. Example cationic surfactants include cetyltrimethylammonium bromide, tetradecyltrimethylammonium bromide, benzalkonium chloride, octadecyltrimethylammonium chloride, cetylpyridinium chloride, dodecyltrimethylammonium chloride, hexadecyltrimethylammonium chloride, and mixtures thereof. Example nonionic surfactants include α-hydro-ω-hydroxypoly(oxyethylene)poly(oxypropyl) poly(oxyethylene) block copolymers, polyoxyethylene ethers, polyoxyethylene sorbitan esters, polyethylene glycol esters of fatty alcohols, and mixtures thereof. Exemplary α-hydro-ω-hydroxy-poly(oxyethylene) poly(oxypropyl) poly(oxyethylene) block copolymers include Poloxamers 182, 184, 231, and mixtures thereof. Exemplary polyoxyethylene ethers include PEG-4 lauryl ether (BRIJ® 30), PEG-2 oleyl ether (BRIJ® 93), PEG-10 oleyl ether (BRIJ® 96), PEG-20 oleyl ether (BRIJ® 99), and mixtures thereof. Example polyoxyethylene sorbitan esters include the monolaurate (TWEEN® 20) the monopalmitate (TWEEN® 40), the monostearate (TWEEN® 60), the monooleate (TWEEN® 80), and mixtures thereof. Example polyethylene glycol esters of fatty acids include polyoxyethylene (8) monostearate (MYRJ® 45), polyoxyethylene (30) monostearate (MYRJ® 51), the polyoxyethylene (40) monostearate (MYRJ® 52), and mixtures thereof.

Suitable amphoteric surfactants include, without limitation thereto, lauramidopropyl betaine, cocamidopropyl betaine, lauryl betaine, cocobetaine, cocamidopropylhydroxysultaine, aminopropyl laurylglutamide, sodium cocoamphoacetate, sodium lauroamphoacetate, disodium lauroamphodiacetate, disodium cocoamphodiacetate, sodium cocoamphopropionate, disodium lauroamphodipropionate, disodium cocoamphodipropionate, sodium lauriminodipropionate, disodium cocoamphocarboxymethylhydroxypropylsulfate, and the like.

In a preferred embodiment, the skin penetration enhancer is an alkyl-2-(N-substituted amino)-alkanoate, an (N-substituted amino)-alkanol alkanoate, or a mixture of these. For convenient reference, alkyl-2-(N-substituted amino)-alkanoates and (N-substituted amino)-alkanol alkanoates can be grouped together under the designation alkyl-(N-substituted amino) esters.

A preferred penetration enhancer comprises an N,N-di(C_1-C_8) alkylamino substituted, (C_4-C_{18}) alkyl (C_2-C_{18}) carboxylic ester or pharmaceutically acceptable acid addition salt thereof. As used herein, the term "(C_4-C_{18}) alkyl (C_2-C_{18}) carboxylic ester" means an ester of a (C_4-C_{18}) alcohol and a (C_2-C_{18}) carboxylic acid. The term "N,N-di(C_1-C_8) alkylamino substituted," in reference to a (C_4-C_{18}) alkyl (C_2-C_{18}) carboxylic ester means that either the alcohol portion or the carboxylic acid portion from which the ester is prepared bears an amino substituent NR_xR_y, wherein R_x and R_y are each independently a (C_1-C_8) alkyl group. Preferably R_x and R_y are both methyl groups.

Preferred are dodecyl-2-(N,N-dimethylamino)-propionate (DDAIP); dodecyl-2-(N,N-dimethylamino)-acetate (DDAA); 1-(N,N-dimethylamino)-2-propyl dodecanoate (DAIPD); 1-(N,N-dimethylamino)-2-propyl myristate (DAIPM); 1-(N,N-dimethylamino)-2-propyl oleate (DAIPO); and pharmaceutically acceptable acid addition salts thereof. DDAIP is available from Steroids, Ltd. (Chicago, IL). The preparation of DDAIP and crystalline acid addition salts thereof is described in U.S. Pat. No. 6,118,020 to Büyüktimkin, *et al.*, which is incorporated herein by reference. Long chain similar amino substituted, alkyl carboxylic esters can be synthesized from readily available compounds as described in U.S. Pat. No. 4,980,378 to Wong, *et al.*, which is incorporated herein by reference to the extent that it is not inconsistent herewith.

Non-limiting examples of solvents include aliphatic esters such as triethylcitrate (TEC), aromatic esters, such as diethylphthalate (DEP), dipolar aprotic solvents, N-methyl-2-pyrrolidone (NMP), diethylene glycol monoethyl ether (DGME), dimethyldecylphosphoxide, methyloctylsulfoxide, dimethyllaurylamide, dodecylpyrrolidone, dimethylacetamide, dimethylsulfoxide,

decylmethylsulfoxide, dimethylformamide, oils such as squalane, and the like which affect keratin permeability.

Particularly preferred skin permeation enhancers are DGME, DDAIP, TEC, TEG, DEP, NMP, oleic acid, lauryl alcohol, propylene glycol, ethyl acetate, and combinations thereof.

Pressure-sensitive adhesives (PSAs) are well known materials that preferably can be adhered to a substrate by application of a relatively light force and, when removed, leave substantially no residue. The major classes of PSAs are composed of polymers, such as acrylics, silicones, and isobutylenes. In the present transdermal delivery system, the PSA component provides for intimate contact of the drug-containing skin adhesive and the skin surface for maintaining controlled and sustained transdermal release of the drug.

The adhesive component is not limited as long as it is physiologically tolerable to human skin and can dissolve and maintain tulobuterol dissolved therein in a crystal-free form, i.e., no crystals are visually or microscopically observable in the adhesive formulation. In patch embodiments, the adhesive may constitute an amount in the range of about 1% to about 99% of the total weight of the total skin adhesive composition, preferably about 2% to about 90%, and more preferably about 50% to about 85%; the amount of adhesive being dependent on the amount of drug and other formulation components.

A preferred adhesive is an acrylic-based polymer, such as any of the homopolymers, copolymers, terpolymers, and the like of various acrylic acids known in the pressure-sensitive adhesive arts. Exemplary acrylate polymers include, but are not limited to, polymers of one or more monomers of acrylic acids and other copolymerizable monomers. The acrylate polymers also include copolymers of alkyl acrylates and/or methacrylates and/or copolymerizable secondary monomers or monomers with functional groups. By varying the amount of each type of monomer added, the cohesive properties of the resulting acrylate polymer can be changed as is known in the art.

Acrylate monomers which are generally used include acrylic acid, methacrylic acid, butyl acrylate, butyl methacrylate, hexyl acrylate, hexyl methacrylate, 2-ethylbutyl acrylate, 2-ethylbutyl methacrylate, isooctyl acrylate,

isooctyl methacrylate, 2-ethylhexyl acrylate, 2-ethylhexyl methacrylate, decyl acrylate, decyl methacrylate, dodecyl acrylate, dodecyl methacrylate, tridecyl acrylate, and tridecyl methacrylate. Functional monomers, copolymerizable with the above alkyl acrylates or methacrylates, which are generally used include acrylic acid, methacrylic acid, maleic acid, maleic anhydride, hydroxyethyl acrylate, hydroxypropyl acrylate, acrylamide, dimethylacrylamide, acrylonitrile, dimethylaminoethyl acrylate, dimethylaminoethyl methacrylate, tert-butylaminoethyl acrylate, tert-butylaminoethyl methacrylate, methoxyethyl acrylate and methoxyethyl methacrylate. Detailed examples of acrylic adhesives suitable in the practice of the invention are described in Satas (ed.), "Acrylic Adhesives," *Handbook of Pressure-Sensitive Adhesive Technology*, 2nd ed., pp. 396-456, Van Nostrand Reinhold, New York (1989).

Other suitable adhesive materials for the skin adhesive layer may include, polysiloxanes, polyisobutylenes, polyurethanes, plasticized ethylenevinyl acetate copolymers, low molecular weight polyether amide block polymers (e.g., PEBAX), tacky rubbers, such as polyisobutene, polystyrene-isoprene copolymers, polystyrene-butadiene copolymers, and mixtures thereof.

Preferred adhesive materials for use in the skin adhesive layer are polyacrylates, polystyrene-isoprene block copolymers, polyisobutylenes, amine-compatible and standard silicones, and polyurethane, with polyacrylates and tacky rubbers particularly preferred. Exemplary acrylic adhesives are commercially available and include a series of polyacrylate adhesives sold under the trademarks GELVA® Multipolymer Solution as GMS grades 2873, 3067, 3083, and 3235 by UCB Group, and pressure sensitive adhesives sold under the trademarks DURO-TAK® 80-1194, DURO-TAK® 80-1196, DURO-TAK® 80-1197, DURO-TAK® 87-2516, DURO-TAK® 87-2194, DURO-TAK® 87-2353, DURO-TAK® 87-2196, DURO-TAK® 87-9301, and the like sold by National Starch and Chemical Corporation. Example silicone pressure-sensitive adhesives include the amine-compatible BIO-PSA® 4200 Series and the standard BIO-PSA® 4500 Series sold by Dow Corning Corporation. A suitable rubber adhesive is styrene-isoprene-styrene (SIS) block copolymer, available under the trademarks QUINTAC® 3433 from Nippon Zeon (Japan) and CARIFLEX™TR-1107 from Shell Kogaku K.K.

Particularly preferred is GELVA® Multipolymer Solution, GMS grade 3083, an acrylic resin solution which, according to the manufacturer, is a copolymer of 2-ethylhexylacrylate and methacrylate designed with no functional monomers for pressure sensitive adhesives. GELVA® 3083 solution is available at a total solids content of about 37.5% in ethyl acetate, having a Brookfield viscosity of about 4800 milli-Pascal seconds (mPa•s), a shear rate of about 37.8 minutes, and reportedly typically provides a 180° peel strength of about 2.5 pounds/inch width at a 20 minute bond time for polyester film to stainless steel (1 mil (25.4 μm) dry adhesive on 1 mil film).

GELVA® 3067 solution is available at a total solids content of about 47.9% in ethyl acetate, having a Brookfield viscosity of about 32,050 (mPa•s), and a shear rate in the range of about 5 to about 15 minutes. GELVA® 3235 solution is available at a total solids content of about 37.6% in ethyl acetate, having a Brookfield viscosity of about 11,140 (mPa•s), a peel strength of about 0.4 pounds/inch, and a shear rate in the range of about 50 to about 90 hours. Thus, GELVA® 3067 has a higher tack adhesion and a lower shear and GELVA® 3235 has a lower adhesion and higher shear than GELVA® 3083. GELVA® 2873 reportedly has acid functionality.

Also preferred is DURO-TAK® 87-2516, an acrylate-vinyl acetate, self curing pressure sensitive adhesive supplied at a total solids content in the range of about 40 to about 43% in an organic solvent solution which according to the manufacturer is typically composed of about 63% ethyl acetate, about 27% ethanol, about 8% heptane, and about 2% methanol, and reportedly typically provides a 180° peel strength in the range of about 25 oz/inch (10 N/25mm) at a 20 minute bond time and about 80 oz/inch (22 N/25mm) at a one week bond time. Also preferred is DURO-TAK® 87-9301, an acrylic, non-curing pressure sensitive adhesive, containing no vinyl acetate or functional monomers, supplied at a total solids content of about 40% in an organic solvent solution which according to the manufacturer is composed of 100% ethyl acetate, and reportedly typically provides a 180° peel strength in the range of about 52 oz/inch (14 N/25mm) at a 20 minute bond time, and a tack (Loop) of 45 oz/in^2 (12 N/25mm^2). Other preferred DURO-TAK® pressure-sensitive adhesives are DURO-TAK® 87-2194, an acrylate-vinyl

acetate self-curing PSA supplied at a solids content of about 45% in an organic solution, which according to the manufacturer contains about 46% heptane, about 21% xylene, about 15% ethylacetate, about 10% isopropanol, about 7% toluene and about 1% 2,4-pentanedione, and DURO-TAK® 87-2353 an all-acrylic non-curing PSA supplied at a solids content of about 36.5% in an organic solution which according to the manufacturer contains about 87% ethylacetate and about 13% hexane. According to the manufacturer each of the foregoing PSAs reportedly typically provides a 180° peel strength in the range of about 55 oz/in (15 N/25mm) at a 20-minute bond time and about 75 oz/in (21 N/25mm) at a one-week bond time.

A preferred amine-compatible, medium tack, silicone pressure-sensitive adhesive is a methylated trimethylated silica sold under the trade name, BIO-PSA® 7-4202 Silicone Adhesive by Dow Corning Corporation supplied at a solids content of about 60% in ethyl acetate, reportedly having a peel adhesion of about 900 g/cm.

Optionally, the skin adhesive composition may include a plasticizer or tackifying agent in the formulation to improve the adhesive characteristics of the composition. Suitable tackifying agents are known in the art and generally include aliphatic hydrocarbons; mixed aliphatic and aromatic hydrocarbons; aromatic hydrocarbons; substituted aromatic hydrocarbons; hydrogenated esters; polyterpenes; rosin esters, hydrogenated wood rosins, and the like. The tackifying agent employed is preferably compatible with the adhesive. An exemplary tackifying agent is silicone fluid (e.g., 360 Medical Fluid, available from Dow Corning Corporation, Midland, Mich.), mineral oil, or rosin ester (e.g., KE-311 available from Arakawa Chemical Co., Osaka, Japan).

Patches prepared with a transdermal tulobuterol skin adhesive composition of this invention can be prepared to provide any desired active dimensional surface area. A useful area may be in the range of about 1 to about 15 square centimeters (cm^2), preferably in the range of about 2 to about 12 cm^2. Preferably the transdermal patches have a drug load in the range of about 0.01 to about 2 mg/cm^2, more preferably in the range of about 0.1 to about 0.4 mg/cm^2.

The transdermal tulobuterol skin adhesive compositions of this invention can be produced by a variety of methods known in the preparation of

drug-containing adhesive preparations, including the mixing of a polymeric adhesive, drug, and additional excipient ingredients in solution, followed by removal of the processing solvents. The drug-in-adhesive delivery system of this invention permits inclusion of therapeutically effective amounts of the tulobuterol drug directly within the skin-contacting adhesive formulation of a patch, while maintaining acceptable transdermal delivery of the tulobuterol, and acceptable tack, and peel adhesive properties of the delivery device. In a patch device aspect of the invention, the skin adhesive composition can comprise a single layer, drug-in-adhesive monolithic device or can comprise an adhesive portion of any other type of transdermal drug delivery device (e.g., a reservoir device). A single layer, drug-in-adhesive monolithic device embodiment is preferred.

A patch, or individual dosage unit, of the present invention can be produced in any manner known to those of skill in the art. After the skin adhesive composition is formed, it may be brought into contact with the backing layer in any manner known to those of skill in the art. Such techniques include calender coating, hot melt coating, solution coating, etc.

FIG. 1 is a schematic illustration of an single-layer drug-in-adhesive patch embodiment of the invention. The delivery system comprises a monolithic body 10 of a defined geometric shape with a protective release liner 14 on one side of the monolithic body 10 and a backing layer 16 on the other side. Removal of the release liner 14 exposes the pressure-sensitive drug-in-adhesive matrix 12 which functions both as the drug carrier matrix and as the means of applying the drug delivery system to the skin of the patient. The backing 16 is substantially coterminous with the drug-in-adhesive matrix 12. The liner 14 is substantially coterminous with the drug-in-adhesive matrix 12 and may be configured or adapted to include a finger hold for grasping and aiding in removal of the liner therefrom.

The backing functions as the primary structural element of the device and provides the patch with flexibility, drape and, preferably, controlled occlusivity. The material used for the backing layer is inert and incapable of absorbing drug, enhancer or other components of the pharmaceutical composition contained within the device. The backing may be made of one or more sheets or films of a flexible material that serves as a protective covering to prevent loss of

drug or vehicle or both by transmission through the upper surface of the device, and imparts a desired degree of occlusivity to the device, such that the area of the skin covered on application becomes hydrated. The material used for the backing layer may permit the device to follow the contours of the skin and be worn comfortably on areas of the skin, such as at joints or other points of flexure, that are normally subjected to mechanical strain with little or no likelihood of the patch disengaging from the skin due to differences in the flexibility or resiliency of the skin and the device. Preferably, the backing is sufficiently flexible to conform to the skin area on which the patch is applied and be worn comfortably with little or no likelihood of the patch disengaging from the skin due to differences in the flexibility or resiliency of the skin and the device.

The backing material should be substantially inert, i.e., non-reactive with the ingredients of the formulations. The backing can be occlusive, semi-occlusive, or non-occlusive (breathable), depending on the amount of moisture vapor transmission rate (MVTR) desired. Methods of measuring MVTR are well known in the art, and a description is found, for example, in U.S. Patent No. 5,702,720 to Effing, *et al.*, the relevant disclosures of which are incorporated herein by reference. A standard value of cutaneous insensible perspiration, representing loss of water from living skin, has been regarded to be about 16 $g/m^2/hr$ as reported in Kuno, Yas, *Human Perspiration*, Ch.1, pp. 26-27, Charles C. Thomas Publisher, (Springfield, IL, 1956). Based on this water loss value, Effing, *et al.*, in U.S. Patent No. 5,702,720 estimated the daily MVTR of living skin to be about 400 $g/m^2/24$ hours (hrs). Devices that have a MVTR substantially below this value, therefore, are generally described as occlusive and those having a MVTR value substantially greater than 400 $g/m^2/24$ hrs are described as non-occlusive. A presently preferred occlusive backing has a MVTR value of not more than about 200 $g/m^2/24$ hours; more preferably of not more than about 75 $g/m^2/24$ hrs, and most preferably of not more than about 50 $g/m^2/24$ hrs.

A presently preferred substantially semi-occlusive backing has a MVTR value in the range of about 400 $g/m^2/24$ hrs to not more than about 1,000 $g/m^2/24$ hrs. A presently preferred substantially non-occlusive backing has a

MVTR value in the range of about 1,000 g/m²/24 hrs. to not more than about 1,500 g/m²/24 hrs.

Backing materials are well known in the art and can comprise films or sheets of polyesters; such as polyethylene terephthalate (PET); polyolefins, such as polyethylene, polypropylene and copolymers thereof; vinyl acetate resins, such as ethylene/vinyl acetate copolymers (EVA), ethylene-ethylacrylate copolymer (EEA), vinyl acetate-vinyl chloride copolymers, vinylon, and the like; polyamides, polyvinyl chlorides, polyvinylidene chlorides, polyurethanes, such as spandex (SPDX); celluloses, such as cellulose acetate, ethyl cellulose, cotton, rayon, and the like; metal foils, such as aluminum; and laminate combinations thereof. Backing materials can be woven fabric, non-woven fabric, elastomeric fabric, knitted fabric, spun-bonded fabric, and combinations thereof.

Exemplary backing materials include polyester film laminates sold by 3M under the trade names SCOTCHPAK™ 9732 (polyester laminate with a (9%) ethylene vinyl acetate heat seal layer having a nominal caliper thickness of 2 mils. (50.8 μm) and a reported Moisture Vapor Transmission Rate (MVTR) of 15.5 g/m²/24 hrs; SCOTCHPAK™ 9733 (polyethylene with (12%) ethylene vinyl acetate having a nominal caliper thickness of 2 mils (50.8 μm) and a reported MVTR of 17 g/m²/24 hrs; SCOTCHPAK™ 9735 (polyester with (12%) ethylene vinyl acetate heat-seal layer), having a nominal caliper thickness of 2 mil (50.8 μm) and a reported MVTR of 7 g/m²/24 hrs; SCOTCHPAK™ 9723 (polyethylene and polyester laminate heat-seal layer having a nominal caliper thickness of 1.7 mil (43.2 μm) and a reported MVTR of 12 g/m²/24 hrs; and SCOTCHPAK™ 1109 (pigmented polyethylene and aluminum vapor coated polyester having a nominal caliper thickness of 1.3 mils (33 μm) and a reported MVTR of 0.3 g/m²/24 hrs. Another exemplary occlusive backing is a non-woven cotton and PET laminate fabric having a MVTR of about 200 g/m²/24 hrs. sold by Nichiban KK.

Other exemplary occlusive backing materials are a non-woven material sold by 3M under the tradename COTRAN™, such as COTRAN™ 9720 polyethylene monolayer film having a reported MVTR of 9.4 g/m²/24 hrs; COTRAN™ 9722 polyolefin monolayer film having a reported MVTR of 7.9

g/m²/24 hrs; COTRAN™ 9726 ethylene vinyl acetate (EVA) having a reported MVTR of 18.1 g/m²/24 hrs, and the like.

Exemplary semi-occlusive backings are a polyurethane film sold by Nichiban KK having a MVTR value of about 405 g/m²/24 hrs, and a polyurethane film sold by 3M under the tradename COTRAN™ 9701 having a reported MVTR value of 709 g/m²/24 hrs. An exemplary non-occlusive, non-woven backing material is a cotton fabric, sold by Nichiban KK, having a MVTR value of about 1205 g/m²/24 hrs. Another exemplary backing sold by 3M under the tradename COTRAN™ 9700 is a melt-blown polyurethane having a reported MVTR value of 8408 g/m²/24 hrs. Other non-woven backings can be a biaxially oriented polypropylene (BOPP) or polypropylene having multidirectional stretch, such as the backing sold by 3M under the tradenames COTRAN™ 9725 and COTRAN™ 9729 and elastomeric fabrics, such as spandex (SPDX). An exemplary elastomeric fabric is Lycra spandex having a MVTR value of about 1352 g/m²/24 hrs. Other suppliers of suitable polyurethane and non-woven backing materials are known in the art.

A preferred occlusive backing material is a polyester/EVA laminate (3M™ SCOTCHPAK™ 9732). A preferred substantially semi-occlusive, backing may be rayon, vinylon, or a PET-lined non-woven fabric. Preferred substantially non-occlusive backing materials include polyurethane and non-woven fabrics.

Backing materials are well known in the art and can comprise films of polyesters, polyethylene, polypropylene, polyamides, vinyl acetate resins, ethylene/vinyl acetate copolymers, polyvinyl chloride, polyurethane, and the like, and combinations thereof, metal foils, non-woven fabric, cloth and commercially available laminates. A useful backing material generally has a thickness in the range of 2 micrometers to 1,000 micrometers, preferably in the range of about 15 micrometers to about 70 micrometers, more preferably in the range of about 30 micrometers to about 60 micrometers.

The release liner is a disposable element which protects the device prior to application. Typically, the release liner is formed form a material impermeable to the drug, vehicle and adhesive, and which is easily stripped from the contact adhesive. The release liner is occlusive and functions to protect the

surface of the drug-in-adhesive layer during production, storage, and transport.

Suitable release liners are well known in the art and are commercially available. Release liner materials are generally occlusive sheet materials, such as webs or films of polyester, poly(vinyl chloride), poly(vinylidene chloride), polyethylene, polyethylene terephthalate (PET), ethylene/vinyl acetate copolymers (EVA) polystyrene and the like, paper (e.g. wood-free paper and glassine paper), and laminate films of paper and polyolefin, metal foils, and the like. Release liners are preferably subjected to a release treatment, such as silicone or fluoropolymer treatment, on the surface of the liner that comes in direct contact with the skin adhesive matrix of the transdermal patch. Silicone-coated polyester, fluoropolymer-coated polyester, and silicone-coated aluminum are typically preferred. Where a polysiloxane is part of the adhesive system, the release liner must be compatible with the silicone adhesive.

Exemplary liners include, without limitation, fluoropolymer coated polyester film sold by 3M under the trade names SCOTCHPAK™ 1022 Release Liner reportedly having a caliper nominal thickness of 3 mils (76.2μm) and a liner release force of <100g/in (<1.0 Newtons/25.4 millimeters (mm)); SCOTCHPAK™ 9742 having a nominal thickness of 5 mils (127 μm); and SCOTCHPAK™ 9744 reportedly having a nominal caliper thickness of 3 mils (76.2 μm) and a liner release force of <100g/in (<1.0 Newtons/25.4 millimeters (mm)). Other exemplary liners include a silicone-coated PET liner sold under the trade name MEDIRELEASE® by Mylan Technologies Inc., silicone-coated polyester film sold in various liner grades by Loparex Inc, and liner films sold under trade names BIO-RELEASE® and SYL-OFF® 7610 by Dow Corning Corporation. A preferred release liner film is a silicone-coated PET, such as MEDIRELEASE® 2249 available from Mylan Technologies Inc., reportedly having a nominal caliper thickness of 3 mils (76.2 μm) and a nominal liner release force value of 14 g/in (14 g/2.54 cm).

A useful release liner generally has a thickness in the range of about 12 to about 500 micrometers, preferably about 50 to about 400 micrometers, more preferably about 60 to about 150 micrometers.

The configuration of the transdermal delivery system of the present invention can be in any shape or size as is necessary, desirable, or practical. Illustratively, a single dosage unit may have a surface area in the range of 1 to 100 cm^2. Preferred active dosage surface areas sizes are in the range of about 1 to about 30 cm^2, more preferably in the range of about 2 to about 15 cm^2.

A transdermal patch, or individual dosage unit, of the present invention can be produced in any manner known to those of skill in the art. The skin adhesive composition is first formulated as a water-insoluble, liquid solution, referred to herein as a "wet-base" solution. After the wet-base solution is formulated, it may be cast on a support, such as a release liner, substantially dried to remove unwanted volatile processing solvent and provide a drug-in-adhesive (DIA) matrix, which is then brought into contact with a second support, such as the backing layer, in any manner known to those of skill in the art. Such techniques include calender coating, hot melt coating, solution coating, etc.

An exemplary general method of preparation of single layer, drug-in-adhesive transdermal patches is as follows:

1. Appropriate amounts of pressure-sensitive adhesive, such as acrylic acid-based or rubber-based, or silicone-based adhesive, dissolved in an appropriate solvent, is placed in a mixing vessel;

2. The drug is then added to the adhesive mixture and mixing agitation is carried out until the drug is uniformly incorporated therein to provide a DIA mixture.

3. Penetration enhancer, and any optional co-solvent and excipients, is then added to the drug-adhesive mixture, and thoroughly mixed to provide a wet-base formulation.

4. The wet-base formulation is permitted to de-aerate, as necessary, and is then transferred to a coating operation where it is uniformly cast or coated onto a release liner at a controlled specified thickness by any conventional technique, such as pouring, brushing, spraying, and the like to provide a DIA coating.

5. The DIA coated product is then substantially dried, such as by passing through an oven, preferably at a temperature of not more than about 80 °C, to drive off all unwanted volatile processing solvents to provide a substantially dried DIA matrix.

6. The substantially dried DIA matrix on the release liner is then laminated to the backing material by any conventional laminating technique, such as rolling under uniform pressure, and wound into rolls or folded into sheets for storage or further manufacture of patches.

7. Appropriately sized and shaped dosage units may be die-cut from the roll or sheet material and then packaged, such as in a heat sealed pouch or packet.

In step 2, the drug is preferably solubilized in ethyl acetate before adding the drug to the adhesive mixture. In step 4, the thickness of the cast wet-base formulation is preferably in the range of about 100 to about 400 micrometers on the release liner. In step 5, drying is preferably carried out at a temperature of not more than about 70 °C, the dried DIA matrix preferably has a thickness in the range of about 12 to about 250 micrometers.

The order of the process steps, the amounts of ingredients, and the amount and time of mixing agitation are process variables which will depend on the specific amounts of adhesive, drug, penetration enhancers and other excipients used in the formulation. For example, steps 1-3 may be performed concurrently or sequentially, or, in step 4, the formulation may be cast onto the backing material in which case, in step 6, the dried product may be laminated onto the release liner. The process factors can be readily adjusted by those of skill in the art as required to provide a uniform product which has acceptable pressure-sensitive adhesive characteristics without sacrificing acceptable drug delivery efficacy. Skin permeation may be determined using *in vitro* methods well known in the art using human cadaver skin mounted on either a Franz cell equipped with an auto sampling system or in side-by-side permeation cells.

A therapeutic dose of tulobuterol can be delivered to a mammal, preferably a human, by removing the liner from a dosage unit of the transdermal tulobuterol delivery system, contacting the skin surface with the skin adhesive

DIA matrix and maintaining the contact for a period sufficient to maintain effective bronchodilation therapy.

The transdermal tulobuterol delivery system may be provided for bronchio respiratory tulobuterol therapy in packaged kit form with instructional indicia included therein for use.

Instructional indicia includes, without limitation, printed media, aural media, visual aids, electronic media or a combination thereof which inform and instruct the user. Printed media includes, but is not limited to, labels, pamphlets, books, flyers and the like. Aural media includes, but is not limited to, tape recordings, audio compact disks, records, and the like. Visual aids include, but are not limited, to photographs, slides, movies, videos, DVDs, and the like. Electronic media includes all forms of electronic data storage media, such as, but not limited to, diskettes, interactive CD-ROMs, interactive DVDs, and the like.

The following examples further illustrate the preparation and use of preferred embodiments but are not intended to be limiting.

Examples 1-13

Examples 1-13 illustrate the formulation of transdermal tulobuterol skin adhesive compositions and transdermal patches containing, in the drug-in-adhesive matrix, varying amounts of the drug, varying amounts of penetration enhancers and adhesive, in the amounts indicated in Table 1.

The transdermal tulobuterol delivery patches of this invention were formulated to vary both the drug load and skin permeation enhancer content in the skin adhesive composition. Tulobuterol base was used, and the total tulobuterol content, based on the weight of the skin adhesive composition, was varied in the range of about 2.5 to about 4.5 weight %. The total amount of penetration enhancer in the skin adhesive composition was varied from zero to about 20 weight %. The remainder of the skin adhesive composition was made up of commercial polyacrylate adhesive (GELVA® 3083, about 37.5% total solids in ethyl acetate).

TABLE 1

Patch Example	Tulobuterol Conc'n Weight %	Penetration Enhancer (1) Weight %	Penetration Enhancer (2) Weight %	PAC Adhesive
1	4.5	DGME 5%	DDAIP 5%	QS to100%
2	4.5	DGME 5%	None	QS to100%
3	4.5	None	DDAIP 5%	QS to100%
4	4.5	DGME 10%	DDAIP 10%	QS to100%
5	4.5	NMP 5%	DDAIP 5%	QS to100%
6	4.5	Oleic Acid 5%	DDAIP 5%	QS to100%
7	4.5	None	None	QS to100%
8	4.5	DGME 10%	None	QS to100%
9	4.5	DGME 15%	None	QS to 100%
10	3.5	DGME 5%	DDAIP 5%	QS to 100%
11	2.5	DGME 5%	DDAIP 5%	QS to 100%
12	3.5	DGME 15%	None	QS to 100%
13	3.5	DGME 12.5%	DDAIP 2.5%	QS to 100%

NOTES to Table 1:
PAC: Polyacrylate adhesive, (GELVA® 3083).
NMP: N-Methyl-2-pyrrolidone
DGME: Diethylene glycol monoethyl ether
DDAIP: Dodecyl-2-N,N-dimethylaminopropionate
QS = Quantity sufficient.

The compositions were prepared by mixing the drug, penetration enhancer(s) and adhesive solution together, stirring slowly until all ingredients dissolved, for a period of several hours or until homogeneous, to provide a wet-base solution. The wet-base solution was allowed to de-aerate on standing. Patches were prepared with each of the composition of Examples 1-13, by pouring the wet-base solution onto a release liner (SCOTCHPAK™ 1022, 3M) to provide a wet-base film thickness of about 100 to about 400 micrometers (μm). The cast film was then substantially dried in a laboratory dryer unit at a temperature of not more than about 70 °C for a period sufficient to volatilize the ethyl acetate solvent. The

% tulobuterol load of the dried adhesive coating is shown in Table 1 above, along with the estimated % amount of total penetration enhancer. A backing film (SCOTCHPAK™ 9732, 3M, polyester/EVA laminate) was then laminated onto the substantially dried drug-containing, skin-adhesive coated surface. For use, patches were cut to a dimensional size of about 2 cm x 2 cm square. No crystals were observable in any of the skin adhesive coating layers of the patches of Examples 1-13, based on examination under visible light microscopy.

Example 14

This example illustrates the effective tack and peel adhesion of the transdermal patches prepared with the skin adhesive compositions of Examples 1-13 and the % skin permeation of tulobuterol through human cadaver skin, *in vitro*, relative to that of a commercial transdermal patch, HOKUNALIN® Tape (2 mg dosage) having a dimensional size of about 10 cm^2.

The commercial transdermal HOKUNALIN® patch reportedly controls the release of tulobuterol by utilizing a crystal reservoir of tulobuterol. This technology is described by Yoshihisa, in "Transdermal Patch for Asthma Therapy," *Nitto Technical Report*, V38, No. 2, pp 61-63, published by Nitto Denko, Japan (Dec. 2000). The commercial HOKUNALIN® patch reportedly has a drug content of not less than 5% in the adhesive layer and utilizes isopropyl myristate as the skin permeation enhancer.

Tack adhesion was determined using the Standard Test Method for Pressure-Sensitive Tack of Adhesives using an Inverted Probe Machine, ASTM D2979-01. The release liner was removed from the patch, the patch was mounted on the tester, (Model PT-500, ChemInstruments Probe Tack Tester) and peak removal force was measured in Newton (N) units using a probe having a diameter of 0.5 cm and a probe end area of 0.196 cm^2. Tack adhesion values of at least about 0.5 N, and more preferably greater than about 2 N, are judged acceptable. The results are shown in Table 2, below.

Skin permeation was performed in an *in vitro* using human cadaver skin mounted on a Franz diffusion cell. The human cadaver skin was stored in a deep freezer at a temperature of about -70 °C, and was thawed for use and immersed in 0.9% sodium chloride solution. For testing, the skin was cut into

squares of a dimensional size of about 2 cm x 2 cm. The release liner was removed from the test patch and the skin adhesive surface of the patch was mounted on a square of skin and then the skin was mounted on the permeation cell of a Franz diffusion cell as a permeable membrane. The volume capacity of each of the donor cell and receiving cell was 3 ml, and the permeation area was about 0.64 cm^2. A sample of about 0.15 to about 0.45 ml permeate was collected at each sampling time over a period of about 24 hours, and assayed using HPLC technique. The results are also shown in Table 2.

TABLE 2

Patch of	Tack Adhesion (N)[1]	Relative % Skin Permeation Rate[2]
Ex. 1	3.02 ± 0.11	203
Ex. 2	1.64 ± 0.29	168
Ex. 3	2.74 ± 0.15	136
Ex. 4	2.71 ± 0.16	258
Ex. 5	2.96 ± 0.18	193
Ex. 6	2.77 ± 0.46	161
Ex. 7	1.07 ± 0.14	86
Ex. 8	NT	138
Ex. 9	NT	149
Ex. 10	NT	133
Ex. 11	1.06 ± 0.10	75
Ex. 12	0.98 ± 0.05	110
Ex. 13	0.87 ± 0.10	91

NOTES to Table 2:

1. Peak force in Newtons (0.5 cm diameter probe with probe end area of 0.196cm^2, ChemInstruments Probe Tack Tester, Model PT-500).
2. % Skin permeation rate is relative to that of commercial HOKUNALIN® Tape, 2 mg dosage at 100%.

NT = Not Tested.

Surprisingly, the skin permeation achieved with transdermal tulobuterol delivery systems of this invention containing a drug content in the skin adhesive layer of less than 5% tulobuterol (i.e., not more than 200 $\mu g/cm^2$) was judged equivalent to or greater than that achieved with the commercial transdermal HOKUNALIN® Tape of 2 mg dosage level.

The skin permeation data showed that the permeation rate of tulobuterol through human cadaver skin from the commercial tape was in the range of 5 to 12 $\mu g/cm^2/min$. The permeation rate from the transdermal patches of Examples 12 and 13 was judged substantially equivalent to that of the commercial transdermal patch.

Table 3 compares the relatively low content of tulobuterol in the skin adhesive layer of the patches of Examples 12 and 13, providing an overall drug load ($\mu g/cm^2$) that is judged as substantially similar to that of the 2 mg size commercial HOKUNALIN® Tape, which has a relatively high tulobuterol (not less than 5%) content in the adhesive layer.

TABLE 3

Patch of	Patch[1] Weight(mg/cm^2)	Coating [2] Weight(mg/cm^2)	Drug Load ($\mu g/cm^2$)	Drug[3] Concentration (%)
Ex. 12	22.2	6.8	172	2.7
Ex. 13	21.9	6.4	143	2.1
Commercial	15.8	10 (estimated)	200	not less than 5

NOTES to Table 3:

1. Patch weight includes backing and release liner
2. Coating weight = Dry patch weight - (release liner weight and backing weight).
3. Calculated dry base concentration from assayed drug amount and coating weight.

The % drug release over a period of about 24 hours from the patches of Example 12 and 13 was also determined using the *USP* rotating paddle over disk Apparatus-5 technique disclosed in United States Pharmacopeia XXIII, (*USP*), Drug Release Physical Tests, Chapter 724, Apparatus 5, p. 2018, using water as the

test medium. The results are graphically depicted relative to that of the commercial tape in FIG. 2.

The transdermal layer of patch embodiments of Example 12 and of Example 13 was examined by X-ray Diffraction technique and under a polarizing microscope. No crystals of tulobuterol were found. In contrast, crystals were detected in the transdermal layers of HOKUNALIN® Tapes of 0.5mg, 1mg, and 2mg dose levels under the same examination techniques.

The results show that the transdermal delivery system of this invention permits the inclusion of relatively low amounts (less than 5%) of dissolved tulobuterol (free of crystalline tulobuterol) in the skin adhesive formulation of a transdermal patch without sacrificing tack and peel adhesive properties of the device.

Example 15

The solubility of tulobuterol base in various penetration enhancers was determined by incrementally adding small amounts of the drug to 100 ml of penetration enhancer until the drug no longer dissolved or the amount dissolved exceeded about 30 g/100 ml. The results are shown in Table 4. Solubility was judged as optimal in NMP, DGME, oleic acid, and DDAIP. A particular preferred combination of skin permeation enhancers was DDAIP and DGME. This combination provides increased skin permeation and maintains the drug in dissolved, non-crystalline, form in the adhesive medium.

TABLE 4

Penetration Enhancer	Solubility (g/100 ml.)
PEG-400	5.6
Propylene glycol	2.94
BRIJ® 30	2.31
Oleyl alcohol	2.84
Squalane	0.64
SPAN® 20	0.2
Isopropyl myristate	5.13
NMP	>30
Oleic acid	13.31
DGME	13.24
DDAIP	12.32

NOTES to Table 4:
NMP: N-methyl-2-pyrrolidone
DGME: Diethylene glycol monoethyl ether
DDAIP: Dodecyl-2-N,N-dimethylaminopropionate

Examples 16-21

Examples 16-21 illustrate tulobuterol patches of this invention prepared with a (styrene-isoprene-styrene) SIS rubber-based adhesive (A) system having the composition shown in Table 5.

TABLE 5

SIS Rubber-Based Adhesive A	Wt. % (As Supplied)
Styrene-isoprene-styrene (QUINTAC® 3433)	21
Rosin ester (KE-311, Arakawa)	17.5
Ethyl acetate	61.5

Skin-adhesive formulation (containing Tulobuterol) were prepared with varying amounts of penetration enhancers, DDAIP, DGME, and DGME, and adhesive (A) generally following the procedure described in Examples 1-13, except

that the drug content in the adhesive was constant. The resulting wet-base, rubber-based composition was poured to a thickness of about 400 μm in the release liner and then dried for about 5 minutes at a temperature of about 90°C. The dry load content of the tulobuterol in the adhesive was about 4.5% as shown in Table 6 below, along with the % penetration enhancer and % rubber adhesive (A) indicated. Weight % values are based on the weight of the coating composition after drying.

Also shown in Table 6 is the skin permeation rate and lag time, as well as the relative % permeation rate and relative % lag time compared to that of commercial HOKUNALIN® 2 mg tape.

TABLE 6

Ex.	Drug Conc'n (Wt %)	DDAIP (Wt. %)	DGME (Wt. %)	Adhesive (A) (Wt. %)	Skin Permeation Rate ($mg/cm^2/hr$)	Relative % Permeation Rate[1]	Lag-Time (Hrs.)	Relative % Lag-time[1]
16	4.5		15	80.5	12.7	116	3.59	111
17	4.5	2.5	12.5	80.5	12.6	115	3.30	102
18	4.5		10	85.5	8.4	125	4.97	85
19	4.5		20	75.5	9.7	145	4.55	78
20	4.5		30	65.5	8.6	128	4.34	74
21	4.5		0	95.5	7.5	113	4.88	83

NOTE to Table 6:

1. The value is obtained by comparing the individual value to that of HOKUNALIN® tape, 2 mg dose.

The results show that the relative skin permeation rates of Examples 16-21 were greater than that of the HOKUNALIN® tape. The relative % lag-time was lowest and the skin permeation rate was greatest for Examples 19 and 20, which had the highest concentration of DGME.

A set of patches was prepared using the wet-base composition of patch Example 18, in which the overall drug load was controlled by varying the poured thickness of the wet-base. The approximate dry drug load provided at a 400 μm thickness was about 250 mg/cm^2, at a 300 μm thickness was about 180 mg/cm^2, and at a 200 μm thickness was about 80 mg/cm^2. The results in a skin permeation test over a period of 24 hours compared to HOKUNALIN® 2 mg tape showed the skin

permeation rate increased as the thickness of the poured film, and hence, the drug load increased.

A series of patches were prepared with the wet-base skin adhesive compositions of Examples 16-21, in which the thickness of the poured coating was varied as shown in Table 7 below. Probe tack adhesion was measured in Newtons (N) as described in Example 14 and is also shown in Table 7 along with the thickness of the adhesive layer (coating thickness) after drying.

TABLE 7

Patch Ex.	Poured Thickness (μm)	Patch Thickness (mm)	Tack Adhesion (N)	Dry Coating (mm)
16	400	0.21	1.18	0.083
17	400	0.21	1.33	0.088
18	400	0.21	1.16	0.087
18	300	0.19	1.40	0.062
18	200	0.15	1.29	0.031
19	400	0.2	1.31	0.078
20	400	0.22	1.34	0.09
21	400	0.21	1.42	0.09

NOTE to Table 7:

Coating values are average of 5 patches/Example; coating thickness is calculated as the thickness of the patch less the thickness of the backing and the release liner. Patch thickness is the total thickness of the patch, including the backing and release liner.

Examples 22-27

In examples 22-27, patches of this invention were prepared with various penetration enhancers, N-methyl-2-pyrrolidone (NMP), triethylcitrate (TEC), triethylene glycol (TEG) and diethylphthalate (DEP) employed in the concentrations shown in Table 8. The SIS rubber based adhesive (A) described in Examples 16-21 was employed in the amount shown in Table 8 and the tulobuterol content was about 4.5% in the adhesive layer. Weight percent values are based on the coating of the skin adhesive composition after drying.

TABLE 8

Patch Example	Drug Conc'n (Wt. %)	NMP (Wt. %)	TEC (Wt. %)	TEG (Wt. %)	DEP (Wt. %)	Adhesive (A) (Wt. %)
22	4.5					95.5
23	4.5	10				85.5
24	4.5		10			85.5
25	4.5			10		85.5
26	4.5				10	85.5
27	4.5	10	10			75.5

The rate of skin permeation and lag time, as well as relative % permeation and relative % lag time compared to commercial HOKUNALIN® 2 mg tape was determined and the results are shown in Table 9.

TABLE 9

Patch Example	Skin Permeation Rate ($mg/cm^2/hour$)	Lag Time (Hours)	Relative % Permeation Rate	Relative % LagTime
Commercial	10.6	8.7	100	100
22	9.0	7.2	84.7	82.5
23	9.5	5.5	89.3	63.1
24	9.5	4.6	89.5	52.2
25	10.0	2.1	94.3	24.3
26	10.6	5.1	99.8	58.6
27	12.4	4.5	116.7	51.6

The results show that the penetration enhancers promoted an increase in the skin permeation rate and shortened the lag time.

Examples 28-51

Examples 28-51 illustrate the formulation of transdermal tulobuterol skin adhesive compositions and transdermal patches containing varying amounts of tulobuterol base, varying amounts of penetration enhancers and adhesive, as indicated in Table 10, based on the weight of the substantially dried drug-in-adhesive (DIA) matrix.

The compositions were prepared generally as described in Examples 1-13, except that the tulobuterol base was solubilized in ethyl acetate (about 5 to about 10

weight % based on the weight of the wet-base formulation) before being added to the adhesive composition; and, as shown in Table 10, the concentration of drug was varied in the range of about 1 to about 4.5 weight % and the concentration of penetration enhancer was varied from zero to about 20 weight % based on the dry weight of the DIA matrix.

The penetration enhancers were diethylene glycol monoethyl ether (DGME);dodecyl-2-N,N-dimethylaminopropionate (DDAIP); triethylene glycol (TEG), N-methyl-2-pyrrolidone (NMP); propylene glycol (PG), lauryl alcohol (LA); and oleic acid as indicated.

Three pressure-sensitive acrylic adhesives were studied: GELVA® 3083 (Adhesive A), GELVA® 2873 (Adhesive B), DURO-TAK® 87-2353 (Adhesive C), DURO-TAK® 87-9301 (Adhesive D), and DURO-TAK® 87-2516 (Adhesive E), and one amine-compatible pressure-sensitive silicone adhesive was studied: BIO-PSA® 7-4202 (Adhesive F).

The release liner used for the patches of Examples 28-36 and 42-50 was a fluoropolymer coated polyester film (SCOTCHPAK™ 1022). The release liner used for patch Examples 37-41 was a silicone coated PET liner (MEDIRELEASE® 2249). The backing material used for all patch examples 28-50 was SCOTCHPAK™ 9732, polyester/EVA laminate.

TABLE 10

Patch Ex.	Tulobuterol Weight %	Penetration Enhancer (1) Weight %	Penetration Enhancer (2) Weight %	Adhesive Q.S. to 100%
28	4.5	DGME 14.5%	DDAIP 0.5%	A
29	4.5	DGME 14.5%	DDAIP 0.5%	B
30	4.5	DGME 14.5%	DDAIP 0.5%	C
31	4.5	DGME 14.5%	DDAIP 0.5%	D
32	4.5	None	None	A
33	4.5	TEG 10%	None	A
34	4.5	NMP 10%	None	A
35	4.5	PG 10%	None	A
36	4.5	LA 10%	None	A
37	4.5	None	None	E
38	4.5	NMP 10%	None	E
39	4.5	TEG 10%	None	E
40	4.5	TEG 10%	NMP 10%	E
41	4.5	TEG 20%	None	E
42	4.5	NMP 10%	None	D
43	4.5	TEG 20%	None	D
44	4.5	NMP 10%	None	F
45	4.5	PG 10%	None	F
46	4.5	LA 10%	None	F
47	4.5	None	None	F
48	4.5	Oleic Acid	None	F
49	3	None	None	F
50	2	None	None	F
51	1	None	None	F

The skin permeation rate ($\mu g/cm^2/hr$) was determined by *in vitro* method as described in Example 14; and skin permeation rate relative to that of the commercial HOKUNALIN® Tape (2 mg. dosage) and lag-time (hrs.) was determined for patch Examples 28, 30-39, 42-44, and 47-50. The results are shown in Table 11.

The data for patch Example 29 was not determined. The patch of Example 45 was not tested because the propylene glycol was judged incompatible with Adhesive F. Patch Examples 40, 41, 46, and 51 also were not tested.

TABLE 11

Patch of	Skin Permeation Rate ($\mu g/cm^2/hr.$)*	Relative % Permeation Rate**	Lag-Time (Hrs.)
Ex. 28	12.6	117.2	-3.1
Ex. 30	0.1	1	-8.4
Ex. 31	10.2	95.3	4
Ex. 32	9.2	77.2	1.3
Ex. 33	5.4	54.9	4
Ex. 34	5.3	53.7	4.1
Ex. 35	8.2	83.2	3.7
Ex. 36	7.8	83.2	2.8
Ex. 37	0.5	3.4	6.4
Ex. 38	1.3	9.5	3.3
Ex. 39	14.8	108.9	2.1
Ex. 42	4.8	40.1	4
Ex. 43	5.8	59	4.4
Ex. 44	21.9	133.1	-0.5
Ex. 47	21	127.6	-3.2
Ex. 48	2.3	13.7	6.3
Ex. 49	2.9	22.9	ND
Ex. 50	4.4	34.9	ND

Notes To Table 11:
ND=Not Determined.
* Franz diffusion cell using pH 7.4 phosphate buffered saline medium.
** Relative to that of HOKUNALIN® Tape 2 mg. at 100%.

The patch of Example 39 was judged substantially equivalent to the commercial tape in skin permeation rate but some incompatibility between the drug and Adhesive E in the drug-in-adhesive wet-base formulation was noted resulting in a decrease in available drug activity, suggesting an interaction.

The data illustrate that the skin permeation rate and lag-time can be varied and optimized, as desired, by the appropriate selection of penetration enhancer(s) and adhesives. The lag-time data of Examples 44 and 47, for example, show that the amine-compatible pressure-sensitive silicone adhesive, Adhesive F, provided a rapid release of tulobuterol, which can be mediated by adding penetration enhancer, without the reducing skin penetration rate.

The tack adhesion of patches of Examples 28, 32, 33 and 43 was determined in Newtons by probe tack tester technique as described in Example 14. The results are shown in Table 12.

TABLE 12

Patch of	Tack Adhesion (N)[1]
Ex. 28	0.96 ± 0.7
Ex. 32	1.0 ± 0.1
Ex. 33	0.29 ± 0.2
Ex. 43	1.31 ± 0.16

Note to Table 12:
1. Peak force in Newtons.

The tack adhesion of patch Examples 28, 32 and 43 were judged acceptable. The tack adhesion of patch Example 33 was judged marginally acceptable and was less preferred.

The present invention has been described generally and with respect to preferred embodiments. It will be understood that modifications and variation of the disclosed composition and processes may be made without departing from the spirit and scope of the novel concept of the present invention.

Claims

1. A skin adhesive transdermal tulobuterol composition comprising, on a total composition weight basis, a therapeutically effective amount of less than 5 weight percent total tulobuterol, a skin permeation enhancer, and an effective skin adhesive amount of physiologically tolerable adhesive; the tulobuterol being dissolved in said adhesive.

2. The composition of claim 1 wherein the amount of tulobuterol is in a range of about 1 to about 4.9 weight percent.

3. The composition of any one of claims 1 and 2 wherein the adhesive is a member of the group consisting of an acrylic adhesive, a rubber adhesive, a silicone adhesive, or a combination thereof.

4. The composition of any one of claims 1 through 3 comprising at least two skin permeation enhancers.

5. The composition of any one of claims 1 through 4 wherein the amount of skin permeation enhancer is in the range of about 0.1 to about 40 weight percent.

6. The composition of any one of claims 1 through 5, wherein the tulobuterol is in the free base form.

7. The composition of any one of claims 1 through 6 wherein the composition comprises at least one skin permeation enhancer selected from the group consisting of an aliphatic ester, an aromatic ester, a dipolar aprotic solvent, a carboxylic acid, a polyol, an alcohol, and a carboxylic ester.

8. The composition of any one of claims 1 through 7 wherein the composition comprises at least one skin permeation enhancer selected from the group consisting of N-methyl-2-pyrrolidone, triethylcitrate, triethylene glycol, diethylene glycol monoethyl ether, dodecyl-2-N,N-dimethylaminopropionate, diethylphthalate, oleic acid, propylene glycol, lauryl alcohol, and ethyl acetate.

9. A transdermal tulobuterol delivery system comprising

an inert backing, and a therapeutically effective amount of the skin adhesive compositions of any one of claims 1 through 8 on one surface thereof, the skin adhesive composition providing a skin-contacting surface.

10. The transdermal delivery system of claim 9 including a release liner on the skin-contacting surface of the adhesive composition.

11. A method of delivering a therapeutic dose amount of tulobuterol to a mammal comprising contacting the surface skin of the mammal with the skin adhesive composition of a transdermal tulobuterol system of any one of claims 9 and 10, and maintaining the contact for a period sufficient to provide effective therapy.

12. The method of claim 11 wherein the contact is effected at least once daily.

13. The transdermal tulobuterol system of any one of claims 9 and 10 in packaged form.

14. An article of manufacture comprising a kit for tulobuterol therapy containing the packaged composition of claim 13.

15. The article of manufacture of claim 14 further including instructional indicia for use therein.

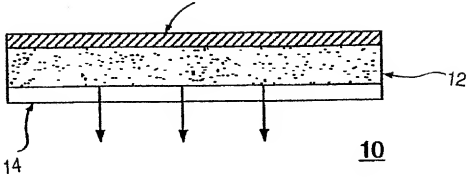

FIG. 1

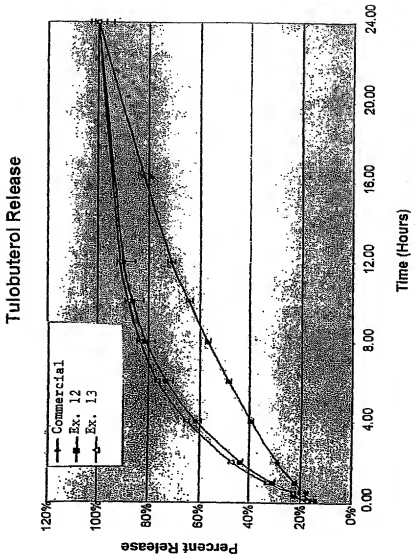
Tulobuterol Release
Commercial
Ex. 12
Ex. 13
120%
100%
80%
60%
40%
20%
0%
Percent Release
0.00
4.00
8.00
12.00
16.00
20.00
24.00
Time (Hours)

FIG. 2

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(54) Title: TRANSDERMAL TULOBUTEROL DELIVERY

(57) Abstract: A transdermal tulobuterol delivery system, preferably in the form of a single-layer, drug-in-adhesive matrix patch, is disclosed comprising a relatively low, (less than five weight percent) concentration of tulobuterol base dissolved in a skin adhesive composition containing at least one skin permeation enhancer. The transdermal delivery system of this invention provides controlled release of the active ingredient, includes a relatively low concentration of tulobuterol within the skin-contacting adhesive formulation of a transdermal patch, and provides acceptable sustained transdermal delivery of the dissolved tulobuterol, as well as acceptable tack and. peel adhesive properties for the delivery device.

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INTERNATIONAL SEARCH REPORT

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,866,157 A (HIGO et al.) 02 February 1999, abstract; col.3, lines 40, 65-67; col.4, lines 1-12; col.5, lines 7-10; col.6, lines 3-8; examples 5, 10, 13, 14.	1-15
X	US2002/0012695 A1 (LEE et al.) 31 January 2002; abstract; paragraphs: 0002,0019-0021, 0030, 0032, 0036, 0037, 0082.	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Janice Ford Isis Ghali Telephone No. (571) 272-1600

INTERNATIONAL SEARCH REPORT

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Continuation of Item 4 of the first sheet:
Examiner suggest:
"TRANSDERMAL TULOBUTEROL DELIVERY"

Continuation of B. FIELDS SEARCHED Item 3:
WEST, ALL DATA BASES
Search terms: tulobuterol, transdermal, adhesive, enhancer